State of TMJ Bioengineering: Working Together Toward Improving Clinical Outcomes

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Abstract: The 6th temporomandibular joint (TMJ) Bioengineering Conference (TMJBC) was held June 14-15, 2018, in Redondo Beach, California, 12 years after the first TMJBC. Speakers gave 30 presentations, and came from the United States, Europe, Asia, and Australia. The goal of the conference has remained to foster a continuing forum for bioengineers, scientists, and surgeons and veterinarians to advance technology related to TMJ disorders. These collective multidisciplinary interactions over the past decade have made large strides in moving the field of TMJ research forward. Over the past 12 years, in vivo approaches for tissue engineering have emerged, along with a wide variety of degeneration models, as well as with models occurring in nature. Furthermore, biomechanical tools have become more sensitive and new biologic interventions for disease are being developed. Clinical directives have evolved for specific diagnoses, along with patient-specific biological and immunological responses to TMJ replacement devices alloplastic and/or bioengineered devices. The 6th TMJBC heralded many opportunities for funding agencies to advance the field: 1) initiatives on TMJ that go beyond pain research, 2) more training grants focused on graduate students and fellows, 3) partnership funding with government agencies to translate TMJ solutions, and 4) the recruitment of a critical mass of TMJ experts to participate on grant review panels. The TMJ research community continues to grow and has become a pillar of dental and craniofacial research, and together we share the unified vision to ultimately improve diagnoses and treatment outcomes in patients affected by TMJ disorders.

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Temporomandibular Joint Bioengineering Conference: Working Together Toward Improving Clinical Outcomes

The sixth temporomandibular joint (TMJ) Bioengineering Conference (TMJBC) was held on June 14–15 2018, in Redondo Beach, California, 12 years after the first TMJBC. Speakers gave 30 presentations and came from the United States, Europe, Asia, and Australia. The goal of the conference has remained to foster a continuing forum for bioengineers, scientists, and surgeons and veterinarians to advance technology related to TMJ disorders. These collective multidisciplinary interactions over the past decade have made large strides in moving the field of TMJ research forward. Over the past 12 years, in vivo approaches for tissue engineering have emerged, along with a wide variety of degeneration models, as well as with models occurring in nature. Furthermore, biomechanical tools have become more sensitive and new biologic interventions for disease are being developed. Clinical directives have evolved for specific diagnoses, along with patient-specific biological and immunological responses to TMJ replacement devices alloplastic and/or bioengineered devices. The sixth TMJBC heralded many opportunities for funding agencies to advance the field: (1) initiatives on TMJ that go beyond pain research, (2) more training grants focused on graduate students and fellows, (3) partnership funding with government agencies to translate TMJ solutions, and (4) the recruitment of a critical mass of TMJ experts to participate on grant review panels. The TMJ research community continues to grow and has become a pillar of dental and craniofacial research, and together we share the unified vision to ultimately improve diagnoses and treatment outcomes in patients affected by TMJ disorders. [DOI: 10.1115/1.4044090]

Introduction

A dozen years after the first temporomandibular joint (TMJ) Bioengineering Conference (TMJBC) [1], the TMJ, or jaw joint, the number of publications have risen (Fig. 1), yet there is still a lack novel diagnostic tools or clinical therapies. The main symptom that leads TMJ patients to seek medical treatment continues to be pain or jaw dysfunction [2–4]. In terms of TMJ research integration with other fields of science, there is still a lack of a strong presence in either the dental or orthopedic fields. The American Association of Dental Research (AADR) and the International Association of Dental Research (IADR) both feature TMJ research in a sporadic and diffuse manner, spread over different research groups. Moreover, the representation of TMJ research in the Orthopedic Research Society (ORS) is even sparser than at the AADR or IADR. Hence, there is an opportunity to promote concentrated/dedicated sessions for TMJ research. Therefore, one of the continuing missions of the TMJBC has been to unite TMJ clinician, veterinarian, engineer, and biologist researchers across disciplines to increase the visibility of the TMJ field.

The format of the TMJBC meeting has evolved from the first to the most recent sixth event[2]. The first conference in 2006 was funded by the National Institute of Dental and Craniofacial Research (NIDCR), with an extensive list of invited speakers documented in a 2007 publication in the *Annals of Biomedical Engineering* [1]. At the sixth TMJBC, speakers were selected from unsolicited abstracts and were then assigned a 15-min oral podium presentation. Presentations at the sixth TMJBC were organized into six areas of emphasis: Clinical studies, biomechanics, natural occurring TMJ disorders in animals, animal models of degeneration, biological basis for disease and treatments, and tissue engineering. There was time for group discussion of each topic, leading to general consensus on the cutting edge of technologies, gaps in the research, and the need for more

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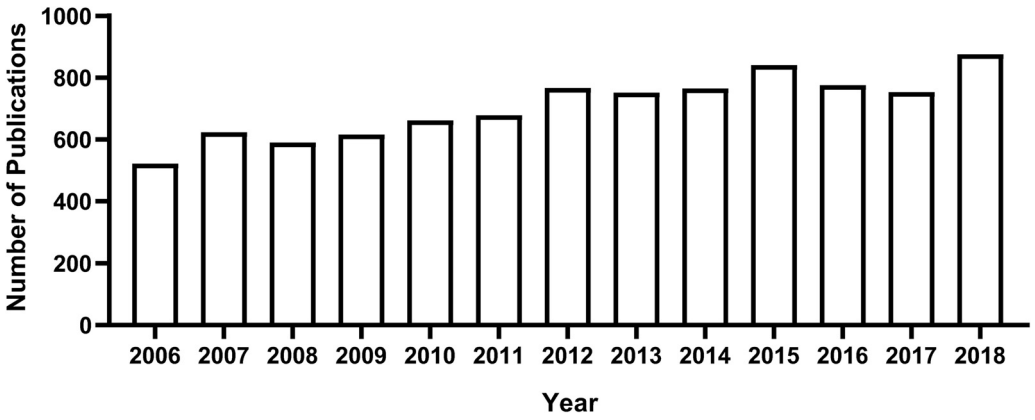

Fig. 1 Number of publications from PubMed with the key terms "TMJ" from 2006 to 2018

standardized clinical and research approaches to the diagnosis and management of TMJ disorders.

The objectives of this publication are to provide an overview of the last conference, to highlight changes in the landscape of publications/grants since the first TMJBC, to attract new talent and established investigators to the field, and to call for policy advancements to grow the TMJ research community. The following sections will summarize the presentations for each area of emphasis and indicate where further advances or greater focus is required.

Clinical Studies Session

The clinical directives that emerged from the five prior TMJBCs have matured. The TMJBCs have been influential in moving surgeons toward a more orthopedic approach to the diagnosis and management of intra-articular TMJ pathology. This orthopedic influence is not only reflected in the abstract presentations at recent TMJBC meetings but also additionally in a contemporary publication entitled "potential indications for tissue engineering in temporomandibular joint surgery" [5] in which the authors, utilizing both their basic science and clinical expertise, developed patient inclusion and exclusion criteria for partial and total TMJ reconstruction using bioengineered tissue.

The following is a synopsis of the clinically related presentations, followed by potential clinical directives that can be drawn from them.

Alloplastic Temporomandibular Joint Replacement. The sixth TMJBC demonstrated the continued expansion of surgeon mindset to include an evidence-based approach to the management of TMJ disorders. This migration was particularly evident in presentations related to the management of end-stage TMJ disease, with the dissemination of preliminary results using three new alloplastic total TMJ replacement systems from Australia, Brazil, and India.

The Australian TMJ replacement system, from Dr. Dimitroulis' group, utilizes a 3D-printed device with a custom-made direct metal laser sintered metal alloy condyle, all polymer digitally sized glenoid fossa, and custom surgical cutting and placement guides. This device was tested in a cohort study in 38 patients, with the longest follow-up reported to be 24 months (mean 15.3 months) [6].

The Brazilian TMJ device, from Dr. Genovesi's group, is an injection-molded TMJ replacement composed of a petroleum-based material: polyether ether ketone (PEEK) LT1 20% Ba. PEEK screws are used to fixate the fossa and short ramus component to the host bone. To date, seven cases at 100 days were reported.

The Indian selective laser melting (SLM), 3D printed, patient-specific TMJ device was reported, by Dr. Mehrotra, to have been developed for the management of TMJ ankylosis and pathology. The fossa component is all-ultrahigh molecular weight polyethylene and the condyle/ramus component was SLM 3D printed titanium alloy. Diet and quality of life variables were improved within 3 months in the patient population reported.

Although presentations at the TMJBC were not all peer-reviewed, the aforementioned presentations emphasize the global need and opportunity for forward-thinking approaches to TMJ total joint replacement, with lessons of the past [1,5] being increasingly more important as the opportunities for clinical translation become within reach with varying regulatory frameworks worldwide.

Biologic and Immunologic Reponses to Temporomandibular Joint Replacement Materials. The potential biologic responses to material wear from alloplastic devices were described in a presentation by Dr. Mercuri, who reported serum metal levels in some maxillofacial reconstruction patients who had undergone dental implant placement, orthognathic surgery using rigid metal fixation plates and screws, or total alloplastic temporomandibular joint replacement. All control participants had levels below the normal reference range for all serum markers assessed. In the orthognathic group, one patient had an increased serum cobalt level. In the TMJ TJR group, one patient had an increased serum cobalt level and another patient had an increased serum chromium level. In the dental implant group, one patient had an increased serum titanium level and another had increased serum levels of titanium and chromium. The results raise questions regarding the types and magnitude of metal released from maxillofacial reconstruction devices and their potential long-term local and systemic effects [7].

Dr. Nadim Hallab, a keynote speaker, discussed immunologic responses to metal particulation due to functional wear associated with TMJ replacement devices, in comparison to hip and knee total joint replacements. Given that $<1\%$ of the $>1 \times 10^6$ people per annum receiving orthopedic total joint replacement implants in the U.S. are not tested for metal sensitivity pre-op or at revision, it is likely that implant-related metal sensitivity has been underreported and remains underestimated. However, the slow and continuing improvements in sensitivity testing will likely continue to provide cumulative clinical evidence into the utility of metal sensitivity testing, along with greater understanding into how and when metal sensitivity develops [8].

Clinical Diagnostic and Therapeutic Studies. Clinical studies related to the diagnosis and management of temporomandibular joint disorders were reported. The results of a diagnostic electromyography (EMG) study from Dr. Connelly's group demonstrated that temporomandibular disorder (TMD) patients had different muscle coordination chewing patterns in the masseter and temporalis muscles compared to normal controls. The TMD patients

demonstrated working-side muscle activity that was significantly less than in the normal controls, possibly due to preferred side chewing patterns. The authors felt these data may provide a reference base for further EMG studies in TMD patients [9].

A study was presented from Dr. Lund's group that examined the extracellular matrix (ECM) proteins in synovial tissue from patients with internal derangement compared to generalized joint hypermobility and normal joint mobility. While the results demonstrated no statistically significant difference in ECM proteins between generalized joint hypermobility and normal joint mobility, patients with internal derangement had significant differences in ECM protein concentrations—indicating TMJ synovial tissue deterioration. These findings may provide synovial fluid markers that might aid in the diagnosis or progressive TMJ disease [10].

The difficulty in the differential diagnosis of TMJ chondromatosis versus chondrosarcoma was presented by Dr. Levorova. Since the treatments and prognoses of these two pathologic entities are completely different, surgeons and pathologists must be aware of this distinction [11].

Therapeutically, results with the use of intra-articular platelet rich plasma (PRP) in the management of TMD pain was presented by Dr. Machon. PRP may effect changes in cell proliferation and regulation of cellular metabolism. This study reported the 5-year follow-up results after PRP injection into the joints of Wilkes IV and V patients. Seven percent of the patients reported no difference in their pain, but 45% experienced the return of their pain within 5 years. The presenter concluded that the major factor in failure of PRP therapy was the duration of patient joint pain before treatment. This study encouraged the important of early diagnosis and management of TMJ pathology [12].

Biomechanics Session

This session provided an update on recent and ongoing biomechanical studies related to the TMJ, mainly with regard to joint loading and its consequences. The first presentation, by Dr. Gallo, addressed the possible mechanical cause of degenerative joint disease and the puzzling gender bias with women being affected by TMJ disorders more often than men in patient studies. TMJ dynamical loading areas were characterized by parameters associated with the energy density spent in the TMJ. In 200 TMJs of females and males (aged 20–40 yr), the data suggested that females performed mandibular movements stressing TMJ soft tissue with a higher energy density than in males. According to Dr. Gallo, this significant difference was due primarily to the smaller volumes stressed in female joints compared to males. Joint incongruity may play a role so that asymmetric mandibular movements likewise increase energy density spent in TMJ soft tissues.

The second contribution, from Dr. Mesnard, presented a novel image processing method for the characterization of cortical and cancellous bone in the mandibular ramus to be used in finite element method (FEM) analyses. This method was developed with the aim of providing patient-tailored information for the design and planning of TMJ replacement device implantation.

Finally, the third communication by Dr. Sagl addressed TMJ modeling concepts with the aim of performing FEM analyses of mechanical loading. The study presented was based on a combination of computed tomography (CT) and magnetic resonance imaging (MRI), thus providing information regarding bone and soft tissues. Soft tissues were studied with MRI at different mandibular positions in order to detect, in particular, TMJ disk and masticatory muscle deformations. By using Hill-type muscle [13] as well as biphasic cartilage models, it was possible to investigate the effects of different movement and force patterns on TMJ loading.

The biomechanics session presented work in progress based on research performed in centers that have traditionally studied the TMJ by developing pioneering methods [14–18]. New data obtained on larger subject samples are providing foundational data showing different loading patterns for different diagnostic groups, in particular, those with myogenous and arthrogenic pain. However, this research needs to be closely connected to those of TMJ tissue biology. Indeed, previous studies have begun looking at soft tissue mechanics, but changes due to tissue degeneration are still greatly understudied. Research mimicking TMJ loading in live tissue and determining its biological response is still in its infancy and would benefit from further investigation.

Natural-Occurring Temporomandibular Joint Damage in Animals Session

In recent years, it has become clear that animals, like humans, develop a spectrum of naturally occurring TMJ disorders such as osteoarthritis (OA), ankylosis, luxation, fracture, and neoplasm [19–21]. Although the anatomic and physiologic features of the TMJ may differ between humans and animals, these naturally occurring diseases may have similar or identical pathogeneses to the disorder in humans [22]. Specifically, studying TMJ disorders that naturally occur in animals may elucidate not only on the pathogenesis of the disorder but also its response to similar therapeutic interventions intended for human use. There were several presentations on naturally occurring TMJ disorders in domestic and wild animals.

Naturally Occurring Temporomandibular Joint Osteoarthritis in Domestic Dogs. Dr. Arzi presented on recent studies examining naturally occurring TMJ disorders in dogs and cats, presenting that TMJ osteoarthritis is most common in dogs when compared to cats [19]. Furthermore, characterization of TMJ osteoarthritis in dogs revealed that, as in humans, the mechanical properties of the TMJ disk are negatively influenced by arthritic conditions as the spectrum of arthritic pathological processes exhibited in dogs include articular surface fibrillation, subchondral bone defects and sclerosis, osteophyte formation, and disk perforation [21]. From a clinical perspective, the manifestation of TMJ osteoarthritis in dogs is similar to humans in the sense that clinical symptoms may not correlate with the presence and severity of CT findings [19,23].

Naturally Occurring Temporomandibular Joint Osteoarthritis in Horses. The horse is a large animal model that experiences naturally occurring TMJ disorders. For example, like humans, horses experience an age-related degeneration in the form of intra-articular disk dystrophic mineralization [24]. In addition, as observed in dogs, cats, and human, horses exhibit TMJ fractures and osteoarthritis. In his presentation entitled "regional and disease-related differences in properties of the equine TMJ disease," Dr. Derek Cissell demonstrated that naturally occurring degenerative changes in the TMJ of horses may impact the compressive stiffness of the TMJ disk in a region-dependent fashion. In addition, he demonstrated that the horse's age, the region of the TMJ, and the specific degenerative changes may all influence the composition and mechanical properties of the equine TMJ disk. These results indicated that future studies should determine how the equine TMJ withstands mediolateral forces during mastication, the consequences of altered TMJ disk composition, and the influence of compressibility for overall joint function and in the pathophysiology of TMJ arthritis in horses.

Naturally Occurring Temporomandibular Joint Osteoarthritis in Wildlife. Dr. Frank Verstraete detailed TMJ arthritis in wildlife via a series of comprehensive studies and publications that examine museum specimens. The most commonly affected species in the western United States include the California sea lion (63.5%), walrus (60.5%), and the American black bear (50%) [25–27]. Interestingly, this particular study found that some carnivores (such as the California bobcat and gray fox) did not exhibit TMJ arthritis [28]. In species that exhibit moderate to serve TMJ arthritis, it is assumed that the disease was associated with a certain degree of discomfort and impaired function. It was concluded

that, while the exact etiology or pathophysiology of TMJ arthritis in wildlife remains elusive, the disease may contribute to morbidity and mortality.

Since naturally occurring disease reflects the complex genetic, environmental, and physiological variation present in the human population, it is plausible that better understanding of TMJ disorders in animals will lead to a better understanding of TMJ disorders in humans, or at least reaffirm existing findings and concepts. On a similar note, clinical trial-based studies utilizing naturally occurring TMJ disorders as a model can be informative for translation of new treatment modalities.

Animal Models of Degeneration Session

The clinical presentation of pain-free TMJ osteoarthritis is often of limited clinical significance. It has been recognized that up to 20% of the population has evidence of TMJ osteoarthritis on imaging without clinical signs or symptoms of disease [29]. Following lower back pain, TMJ discomfort is the second most common musculoskeletal pain disorder with an associated annual cost estimated at $4 billion [30]. Therefore, incorporating pain measures into translational models of TMJ degenerative diseases is critically important.

As with most chronic pain conditions, centralized pain mechanisms often have a greater contribution to the pain syndrome than the initial inciting disease, making it difficult to replicate in animal models [31]. This interplay between centralized pain mechanisms and the inciting disease is evident in the clinical research of TMJ disease with the diagnostic criteria for TMD disease reliance on both axis I characterization of joint and muscle disease and the use of axis II instruments for measuring psychosocial and pain-related disability [32].

In TMJBC 6, only one abstract and one poster specifically addressed animal pain and joint disease models. Dr. Almarza's group presented a poster on whether a sudden change in occlusion is associated with the emergence of hypersensitivity in the TMJ area in adult male rats. These results suggest an increased sensitivity to noxious mechanical stimuli following altered TMJ loading.

An oral presentation by Megan Sperry from Dr. Winklestein's group presented an animal model of TMJ osteoarthritis and pain that utilized mechanical overload to induce condyle changes and pain. In this study, nine rats underwent mechanical loading of their TMJ with 3.5 N of force. The findings suggest hypoxia and inflammation may be early contributors to pain and structural changes in the rat TMJ.

The incorporation of pain assessment in animal TMJ disease models will be important for both the study of acute-to-chronic TMJ pain transition as well as the translation of potential regenerative medicine interventions to clinical care. Further research into the contribution of both central pain mechanisms and peripheral contributions in TMJ animal models of degeneration is urgently needed to better understand the indications and limitation of medical and surgical management of TMJ chronic pain. Indeed, there is a dearth of science on TMJ pain, and the two studies presented are not the only paths to investigate TMJ pain, indicating the need for more pain mechanisms to be investigated.

Biological Basis for Disease and Treatments Session

Dr. Sunil Kapila provided an in-depth presentation highlighting that there are several functional and anatomic distinctions associated with the TMJ when compared to those of appendicular joints. These distinctions may partly explain the challenges in restoring the diseased TMJ to health, or in the engineering of its replacements. First, mandibular condyle fibrocartilage develops from the neural crest rather than from mesodermal origin as does hyaline cartilage in appendicular joints. Second, the mandible, including the condyles, is formed as a secondary cartilage as opposed to primary cartilage as in the formation of appendicular joints and long bones [33]. Third, mandibular condylar fibrocartilage serves a hybrid anatomical function of being both an articular and a growth cartilage, which differs from the appendicular skeleton, where these two functions are served by articular hyaline cartilage and the epiphyseal growth plates, separated by an epiphysis. Finally, while the articular surfaces of appendicular joints are lined by hyaline cartilage, that of the TMJ is composed of fibrocartilage [34], with the mandibular condyle consisting of deeper zones of hyalinelike cartilage that is separated from the more fibrouslike superficial zone (SZ) composed of highly aligned fibers of a proliferative cellular layer [35,36]. Therefore, TMJ fibrocartilage contains both types I and II collagen [37], whereas the articular hyaline cartilage does not typically contain type I collagen [38]. This organization of collagen fiber alignment and type provides the TMJ with the functional characteristic of withstanding tensile loading better than hyaline cartilage. As such, Dr. Kapila explained that the significance of these distinctions to disease initiation and progression between the TMJ and appendicular joints may explain certain genetic disorders that affect every joint in the body while sparing the TMJ [39] as well as the unique age and gender distribution of TMDs [40–44].

Dr. Kapila then presented an overview of his work on pathophysiologic functions of estrogens that primarily involves signaling via estrogen receptors ER-α and ER-β [45]. The preponderance of TMJ problems affects women and their early onset is during reproductive years, as opposed to similar degenerative conditions in other joints that largely afflict postmenopausal women. These findings have led to the implication of female sex hormones, particularly 17-β estradiol (E2) in TMJ osteoarthritis [40,46]. Indirect evidence for an association between E2 and TMJ diseases is provided by findings of elevated serum E2 in subjects with TMJ disease [46,47], the presence of the ERs in the TMJ of females [48], and the association of ER-α polymorphisms that enhance ER-α levels with the prevalence and severity of TMJ OA [49–54]. Dr. Kapila's ongoing studies are exploring in vivo the contributions of E2, ER-α and candidate matrix metalloproteinases to the targeted loss of TMJ matrices and their contribution to TMJ OA specifically, but not of appendicular joint OA.

Additionally, this session highlighted work from Dr. Yadav Sumit's group with three different presentations. The objective of their research effort was to characterize the long-term effects of intermittent parathyroid hormone (I-PTH) delivery on the mandibular condylar cartilage and subchondral bone, in vitro, and in mice. They reported that there was a significant increase in bone volume, tissue density, mineral deposition, tartrate resistant acid phosphatase activity, cell proliferation, and cartilage thickness in the I-PTH treated mice when compared to a control group. In their second presentation, they described the effects of simultaneous injections of the I-PTH and alendronate on the mandibular condylar cartilage and the subchondral bone in a mice model. The findings suggested that the effects of alendronate on mandibular condylar cartilage may be similar to the effects of I-PTH. However, the effects of simultaneous injections of both I-PTH and alendronate were more pronounced in the subchondral bone. The final presentation aimed to determine the effects of bone morphogenetic protein (BMP-2) loss of function on the cartilage and subchondral bone of the TMJ. It was found that deletion of BMP-2 in aggrecan-expressing cells during postnatal development may lead to cartilage breakdown and early development of OA.

The works by Dr. Kapila and Dr. Sumit highlight the need to tailor and design treatment therapies for the TMJ differently than orthopedic joints. PTH based therapies are often targeted for osteoporosis and mainly in females. As such, there is an opportunity to discover similar links between PTH-based therapies and TMJ soft tissues.

Tissue Engineering Session

Since the first TMJBC, the group of investigators focused on TMJ tissue engineering has remained small. The main contributions have come from the original organizers Dr. Athanasiou

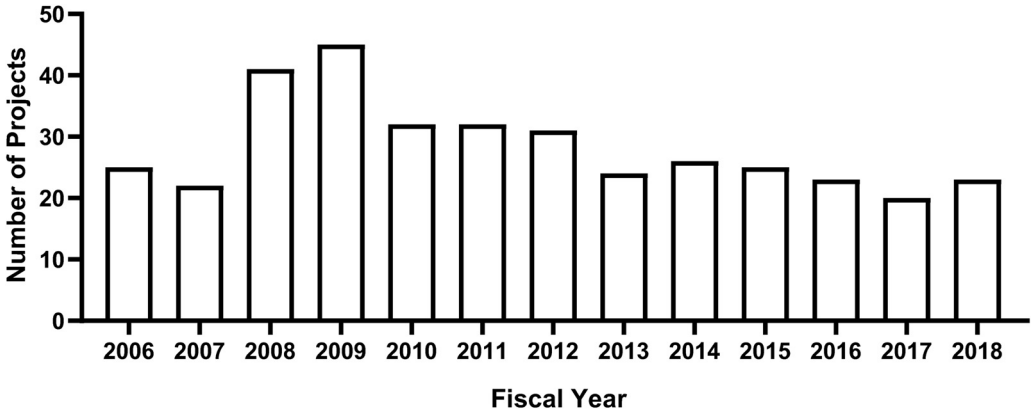

Fig. 2 Number of R01 funded projects from NIH Reporter with the key terms TMJ from 2006 to 2018

[55–58], Dr. Detamore [36,59], Dr. Jeremy Mao [60], Dr. Scott Hollister [61,62], and from Dr. Almarza [63–65]. Nevertheless, profound advances have been made by these researchers in the engineering of both a TMJ disk and mandibular condyle. In terms of the TMJ disk, it now has been shown in animal models that focal defects can be repaired and heal [55], and whole disks can be replaced with scaffold that remodel to become a tissue with many similarities to the native TMJ disk [65]. These studies have shown that both approaches are feasible for the treatment of patients with clinical indications for regenerative therapies. In terms of the mandibular condyle, advances in polymer gradients have regenerated bone in the condyle of rabbits [59] and the soft tissue of the condyle in goats [63]. Overall, these studies draw the field ever closer to create a condyle-disk composite bioengineered replacement implants. Despite these breakthroughs, there are still concerns with the attachment of these implants and their ability to withstand the early shear and torque during mandibular functional loading. More importantly, as discussed elsewhere [5], the patient will need to be selected carefully, as comorbid conditions could play a role in healing. Further, concerns with metaplasia, ossification, and angiogenesis may be considerations for specific patients.

At the sixth TMJBC, presentations were focused on condyle regeneration, mesenchymal stem cells (MSCs) in scaffolds, and a scaffold-free cell sheet for TMJ disk focal defects. Specifically, for mandibular condyle regeneration, Dr. Detamore's Team developed a combinational 3D printer for TMJ tissue engineering of the mandibular condyle that incorporates natural materials, such as devitalized cartilage, demineralized bone, hydroxyapatite, and pentanoate-functionalized hyaluronic acid with polycaprolactone (PCL) to create anatomically precise, patient-specific mandibular condyle bioengineered replacement implants. In these 3D-printed implants, priority was placed on designing both bone and cartilage regions to promote cell-infiltration, with supporting preliminary data presented.

Dr. He's group presented a scaffold-free cell sheet technology to regenerate condylar cartilage by combining bone marrow stromal cells (BMSCs) with condylar chondrocytes. Specifically, high density coculture of these two cells were tested at different ratios (Chondrocyte:BMSC = 10:0,7:3,5:5,3:7,0:10). After 3 weeks of chondrogenesis by micro-environment induction, the 10:0 and 7:3 groups appeared to perform better than the cartilage cell sheets.

In another presentation by Dr. He's group, scaffold-free cartilage cell sheets covering bone marrow mesenchymal stem cells-PCL/hydroxyapatite (BMSCs-PCL/HA) scaffolds (cell sheet group) were transplanted subcutaneously and intramuscularly in minipigs. The biphasic scaffold group appeared to fail in regeneration because of local nonspecific inflammation led by residual and degradation products of the PGA/PLA scaffold, while the cell sheet group appeared to regenerate a healthy osteochondral construct with a mature cartilage layer and closely integrated subchondral structure.

Dr. Helgeland presented work on explaining the effect of the angiogenesis inhibitor, angiostatin, on fibrocartilage formation in an ectopic rat-model. Collagen type-I scaffolds were divided into four groups: (i) scaffold only, (ii) scaffold + BMSCs, (iii) scaffolds + angiostatin, and (iv) scaffolds + angiostatin + BMSCs. Cell was harvested from rat femurs. One construct from each group was randomly, subcutaneously implanted in the dorsa of Lewis rats. After 2 weeks, biomarkers for inflammation, IL-1α and IL-1β and vascularization, CD31 appeared to be down-regulated in constructs functionalized with angiostatin.

Dr. Natalia Vapniarsky, from Dr. Athanasiou's group, presented the first public description of their recent work to develop an innovative surgical method—modeling disk thinning with partial perforation in a minipig. Specifically, they designed and tested a surgical technique for the implantation and stabilization of the engineered tissue in situ, and tested in vivo the efficacy of this tissue-engineered construct to regenerate surgically created TMJ disk defects. As histological evaluation demonstrated that this implantation method resulted in more complete TMJ disk defect closure than in the untreated control TMJ disk defects. The study implantation method induced the formation of fibrous connective repair tissue that filled the TMJ disk defect and this repair tissue was significantly stiffer in tension than similar tissue in the untreated control TMJ disk defects [55].

Dr. Embree's group presented their work on TMJ fibrocartilage stem cells (FCSCs) located below the mandibular condyle SZ, which can self-organize and can regenerate cartilage and bone. In the FCSCs, Wnt/β-catenin signaling inhibits skeletal stem fate to differentiate into chondrocytes and over activation leads to OA, but with the addition of a Wnt inhibitor the FCSC population is maintained and the fibrocartilage is repaired. The group is looking to find the markers that define the TMJ FCSC population and their functional role in differentiation, proliferation, and progression of TMDs.

The current work on TMJ tissue engineering is cutting edge and exciting. However, the small market for TMJ disease management options and devices, compared to orthopedics, presents a barrier to translation. Other technical barriers are also present, such as the efficacy of technologies in a degenerated joint, patient to patient variability, etc. Nevertheless, when these technical challenges are solved, there will always be a "valley of death" in funding to translate TMJ technologies due to the small market. Significant funding will be required from industry partners, private donors, foundations or the NIH (e.g., R01, SBIR/STTR) to derisk these technologies for translation to clinicians and their patients.

Discussion

After six TMJ Bioengineering Conferences, spanning more than 12 years, it is clear that there is a small, but growing and dedicated core of TMJ investigators. This group of investigators

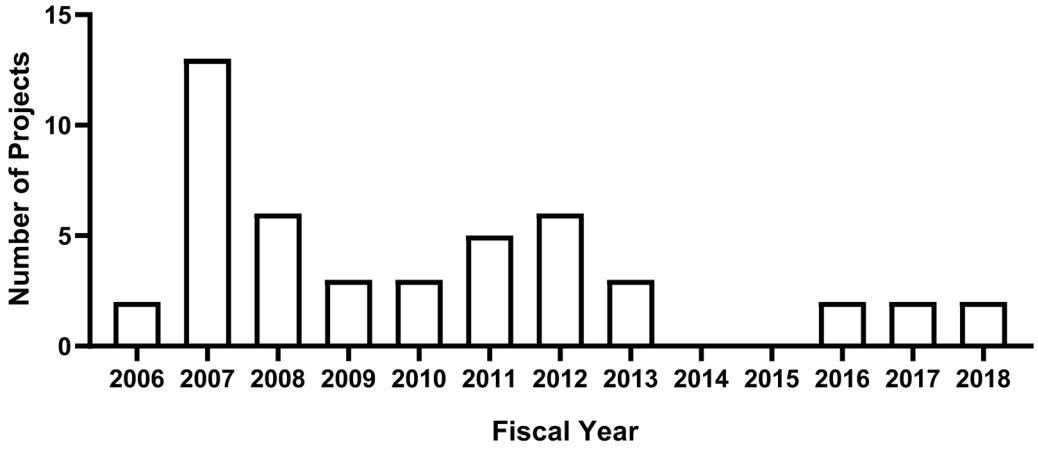

Fig. 3 Number of R21 funded projects from NIH Reporter with the key terms TMJ from 2006 to 2018

have been successful in carrying out many of the directives put forth from the first conference [1], including: Patient specific data, such as metal allergies; more detailed mechanical models of the joint; in-depth studies of the naturally occurring TMJ damage in animals; more biological differences in the TMJ between the sexes and between the TMJ and other joints; biological therapies and mechanisms of disease; and in vivo tissue engineering efforts.

In the discussions during the conference, a lack of standardized research methodologies became apparent. For example, a standard scale to describe the amount of joint damage on histology, such as the OARSI histopathology scale used for cartilage OA, needs to be used as-is or adapted to the TMJ. This scale goes from 0 (pristine) to 6 (full cartilage loss). While the scale can be directly applied to the TMJ condyle, it will have to be modified to describe damage to the disk. Another area of standardization could be mechanical testing, such as displacing at the same percent strain rate to the same strain step for evaluating engineered tissues or establishing target loading values for implanted bone regions for mandibular condyle scaffolds. These changes should be relatively easy to implement as the community is still small and cohesive. Furthermore, standardized outcome measures would assist newcomers to TMJ research in comparing their technologies to the established benchmarks.

Another major topic of discussion was the appropriate target audience for TMJ research, and the sustainability of current efforts. TMJ research is not prominent at the ORS, and in general appears to be more prominent in the dental research community. TMJ podium sessions at the AADR highlight pain, biomechanics, and tissue engineering research. However, TMJ research no longer has a focused research group base at AADR and IADR but is instead spread over many research groups in an ad hoc fashion. As an example, formerly there was the IADR "Neuroscience/TMJ" scientific group, now it is only titled as the "Neuroscience" group. There was additional concern raised about current Federal funding. TMJ grants in tissue engineering, TMJ biomechanics, and TMJ replacement devices are assigned to study sections that do not typically focus on TMJ research, which may make it difficult for reviewers to truly assess the significance and innovation of the proposed work. This can be seen by a decreasing trend of NIH R01 funded projects on TMJ from 2006 to 2018 and almost a 50% drop from 2009 to 2018 (Fig. 2). Furthermore, the low number of NIH R21 projects, with an average of less than two projects per year from 2013 to 2018, indicates a high barrier for entry of new investigators into the TMJ field and the development of new lines of research (Fig. 3).

As the TMJ Bioengineering Conferences move forward, it is hoped that interdisciplinary research continues to grow to bring new diagnostics and therapies to TMJ patients. The group sees many opportunities for the future. First, initiatives at the NIDCR for funding TMJ research have arguably been largely focused on pain as highlighted in "The orofacial pain: prospective evaluation and risk assessment" studies [66–68]. Future request for applications (e.g., requests for applications) should go beyond pain, such as ones that will study joint damage and regeneration, which complements the current NIDCR initiatives. Second, to grow the field, more training grants are needed for graduate students and fellows to become engaged in TMJ science. Third, since TMJ tissue engineering solutions have a small market when compared to orthopedic joints, there is a potential to partner with the Food and Drug Administration for developing translational bioengineered solutions. Lastly, there is room to grow the pool of TMJ experts on grant review panels, to the point that a critical mass of researchers with significant knowledge and experience is able to assess the significance and impact of groundbreaking TMJ research. The past 12 years have seen important new contributions in the TMJ Bioengineering Community, with tremendous opportunity in the next dozen years ahead.

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